



JOURNAL OF PHARMACEUTICAL SCIENCE AND BIOSCIENTIFIC RESEARCH (JPSBR)

(An International Peer Reviewed Pharmaceutical Journal that Encourages Innovation and Creativities)

A Review on Comparison of regulatory guidelines for semi –regulated market for herbal formulation

Vyas Hiral Arunkumar*, Dr. Dilip G. Maheshwari

Department of Quality Assurance and pharm. Regulatory Affairs L.J. Institute of Pharmacy, Ahmedabad Gujarat, India

ABSTRACT:

Majority of the world population even today relies on indigenous system of medicine. There are more than 5000 plants reported, which grows in different part of the world depending upon environmental and geographical conditions required by the plant. Hence in different countries only some of the plant grows naturally and these countries do not have knowledge about safety and efficacy of these herbs. Due to these reason most of the countries have defined their own regulations regarding registration and uses of herbal medicines. Some of the countries have defied very strict guideline which is called regulated countries and some of the countries have somewhat liberal guidelines and these countries are called semi regulated countries.

The work suggest that the different data and certificates required by African region (Nigeria and Kenya) are more or less same but there is difference in their administrative policies, dossier preparation, sample requirement, clinical trial data and hence they take different amount of time to get the product registered.

KEYWORDS: Semi-regulated market, WHO (World Health Organization), COA, FSC, herbal formulation

Article history:

Received 8 Mar 2014

Accepted 16 April 2014

Available online 13 July 2014

INTRODUCTION:

Definition^[1]

Herbal drugs, the natural alternatives for chemical drugs are defined as “the art and science of restoring a sufferer to health by the use of plant remedies”.

According to WHO Nation definitions, herbal medicinal products (medicines) are “medicinal products containing as active ingredients exclusively plant material and/or vegetable drug preparations.”

Herbal drug technology includes all the steps that are involved in converting botanical materials into medicines, where standardization and quality control with proper integration of modern scientific techniques and traditional knowledge will remain important.

CLASSIFICATION OF HERBAL MEDICINE

For practical purposes, herbal medicines can be classified into four categories, based on their origin, evolution and the forms of current usage.

While these are not always mutually exclusive, these categories have sufficient distinguishing features for a constructive examination of the ways in which safety, efficacy and quality can be determined and improved.

For Correspondence:

Ms. Vyas Hiral Arunkumar

*Department of Quality Assurance and pharm
Regulatory Affairs L.J. Institute of Pharmacy,
Ahmedabad Gujarat, India*

Email: hiralvyas27@ymail.com

(www.jpsbr.org)

Categories of Herbal Medicines

Indigenous herbal medicines

This category of herbal medicines is historically used in a local community or region and is very well known through long usage by the local population in terms of its composition, treatment and dosage.

It can be used freely by the local community or in the local region. However, if the medicines in this category enter the market or go beyond the local community or region in the country, they have to meet the requirements of safety and efficacy laid down in the national regulations for herbal medicines.

Herbal medicines in systems

Medicines in this category have been used for a long time and are documented with their special theories and concepts, and accepted by the countries.

For example, Ayurveda, Unani and Siddha would fall into this category of TM.

Modified herbal medicines

These are herbal medicines as described above in categories 1 and 2, except that they have been modified in some way—either shape, or form including dose, dosage form, mode of administration, herbal medicinal ingredients, methods of preparation and medical indications.

They have to meet the national regulatory requirements of safety and efficacy of herbal medicines.

Imported products with a herbal medicine base

This category covers all imported herbal medicines including raw materials and products. Imported herbal medicines must be registered and marketed in the countries of origin.

The safety and efficacy data have to be submitted to the national authority of the importing country and need to meet the requirements of safety and efficacy of regulation of herbal medicines in the recipient country.

Semi-regulated market: ^[2,3]

Semi regulated market is small and medium scale industries that are not completely governed and regulated by the government body.

This market country has own regulatory guideline for register

the product.

List of country: Africa, Latin American Countries, Association of South east Asian Nations (ASEAN) and Commonwealth of Independent States (CIS).

Experts will detail on the current market situation in these countries, regulatory norms for drug registrations, opportunities in various markets, market trends of target countries and guidelines on export strategy to the select countries.

Traditionally, semi-regulated markets (SRM) such as Africa, Asia, CIS and Latin America have been favored export destination for Indian players. However, as significant generic opportunities opened-up in regulated markets (RM) of US and Europe, larger players shifted focus and increased the proportion of exports to these markets

GENERAL REGULATORY AUTHORITY FOR HERBAL PRODUCT. ^[4]

WHO (World Health Organization)

The World Health Organization (WHO) acknowledges it in datedness to the WHO

Member States that provided the information contained in this summary report.

Through the WHO Global Survey on the Regulation of Traditional Medicine(TM) and Complementary/Alternative Medicine (CAM) and the Regulation of Herbal Medicines.

WHO's policy on herbal medicines

The World Health Organization is fully aware of the importance of herbal medicines to many of its Member States and supports the use of medicinal plants and their products.

In early 1978, the World Health Assembly, the WHO governing body, adopted a resolution on drug policies and management of medicinal plants, which recognized the importance of medicinal plants in the health care system.

The World Health Assembly proposed coordinating efforts through the preparation of an inventory of medicinal plants, the development of criteria and methods for proving the safety and efficacy of medicinal plant products, and the dissemination of relevant information.

In four more resolutions were adopted covering the identification, evaluation, preparation, cultivation, utilization, regulation and conservation of medicinal plants.

Based on those resolutions, WHO's policy on herbal medicine may be summarized as follows;

WHO is fully aware of the importance of herbal medicines for the health of a large number of the population in today's world. Herbal medicines are recognized as valuable and readily available resources, and their appropriate use is encouraged.

To promote the proper use of medicinal plants, a comprehensive programme for their identification, evaluation, preparation, cultivation, recognition as valuable and readily available resources, and their appropriate use is encouraged.

It is necessary to make a systematic inventory and assessment (pre-clinical and clinical) of medicinal plants; to introduce measures on the regulation of herbal medicines to ensure quality control of herbal products by using modern techniques, applying suitable standards and good manufacturing practices; and to include herbal medicines in the national standard or pharmacopoeia.

As many of the plants that provide traditional and modern drugs are threatened with extinction, WHO endorses the call for international cooperation and coordination to establish programmes for the conservation of medicinal plants, to ensure that adequate quantities are available for future generations

WHO Regions^[5]

WHO African Region

Regulatory Situation In African Region

Nigeria^[6]

Background information

There has been a rapid expansion of allopathic health care in Nigeria over the last

three decades, including an increase in the number of allopathic health care providers.

At the same time, because the majority of Nigerians use traditional medicine, the

Government of Nigeria has shown appreciation for the importance of traditional

medicine in the delivery of health care.

Regulatory situation

In 1984, the Federal Ministry of Health established the National Investigative Committee on Traditional and Alternative Medicine paying special attention to and providing maximum support for the training ,development, logistic support, and supervision of village health workers and traditional birth assistants, along with the relationship between those workers and their communities and the mechanisms that link those workers to other levels of the health system paying special attention to the involvement of women and grassroots organization of women in the village health system.

In 2000, the Traditional Medicine Council of Nigeria Act was proposed. The functions of the Council include facilitating the practice and development of traditional medicine establishing guidelines for the regulation of traditional medical practice to protect the population from quackery, fraud, and incompetence liaising with state boards of traditional medicine to ensure adherence to the policies and guidelines outlined in the Federal Traditional Medicine Board Act establishing model traditional medicine.

✦ **Kenya**

✦ **Regulatory situation**

Traditional medicine started being incorporated into Kenya's national health policy Frame-work in the late 1970s. Kenya's Development Plan 1989–1993 recognized traditional medicine and made a commitment to promoting the welfare of traditional medicine practitioners.

The Ministry of Health and provincial authorities require the registration of traditional medicine practitioners. In 1999, Kenya's patent law was revised to include protection for traditional medicines.

Table no:1

<u>WHO Region</u>	<u>Country</u>	<u>Regulation(law& Act)</u>
WHO African region	Nigeria	The Federal Ministry of Health Traditional Medicine Council of Nigeria Act
	Kenya	Kenya's national health policy. The Ministry of Health Kenya's medicinal plants

REGULATORY GUIDELINES OF DIFFERENT COUNTRIES**AFRICAN REGIONS****NIGERIA^[7]****A) Administrative data:**

- 1) Application form
- 2) Contract Manufacturing Agreement
 - a) Notarized by a notary public in the country of manufacture.
 - b) Should be signed by both parties stating names and designations of the signatories with the names of all the products to be registered and other relevant clauses clearly explained in an unambiguous language.

B) Documentation

- 1) Free Sale Certificate
- 2) Certificate of analysis
- 3) Certificate of Business Incorporation with the corporate affairs commission in
 - Nigeria
- 4) Certificate of Registration of Brand Name with trademark Registry.
- 5) Applicants shall submit a letter of Invitation to inspect the factory abroad.
- 6) Applicants shall submit dossiers containing relevant information on the products Formats
- 7) Evidence of satisfactory clinical trials conducted in the Country of origin and or
 - any African Country.
- 8) Any other relevant information on the products.
- 9) A permit should be issued if documentation is satisfactory.

C.) Labelling Requirements

- i Name of the product - Generic name, Brand name.
- ii Quantitative list of Ingredients by their Botanical or common names.
- iii Dosage form and Net contents of product.

- iv Directions for use.
- v Indications (shall be on the leaflet) (No claim of cure is permitted until proven through clinical trial).
- vi Batch number, manufacturing date, expiry date.
- vii Storage conditions.
- viii Name and full location address of manufacturer.
- ix Provision for NAFDAC registration / listing number.
- x Specific symptoms of overdose and antidote on the leaflet.
- xi Contra-indications / drug interactions.
- xii Warnings, Precautions. (E.g. use in pregnant and lactating mothers not recommended).
- xiii Disclaimer "These claims have not been evaluated by NAFDAC"
- 3) Any product whose name, package or label bears close resemblance and or is a sound-alike to an already registered/ listed product or is likely to be mistaken for such registered / listed product shall not be considered for registration
- 4) Brand names that a suggestive of therapeutic claims shall not be accepted.

KENYA^[8]**1. APPLICATION FORM**

1.1 The Applicant: The application for the registration of herbal and complementary products shall be made only by:

- The License/patent holder
- The manufacturer
- An authorized Local Technical Representative (LTR) of the manufacturer or License/patent Holder. The name, physical address, telephone number, fax number, and e-mail address of the applicant shall be provided.

1.2 Name of the Local Technical Representative (for imported products only)

Every applicant who is not resident in Kenya shall appoint ONE local technical representative who must be a company incorporated in Kenya and authorized by PPB to deal in herbal and complementary products and must hold a wholesale dealers Licenses

1.3 Declaration by an applicant

The declaration must be signed, dated and authenticated by an Official stamp. No Applications will be evaluated without authenticated declaration.

2. PARTICULARS OF THE MANUFACTURER

2.1 Name of the Manufacturer

2.2 GMP status of the manufacturing site

3. PARTICULARS OF THE PRODUCT

3.1 Product Name

3.2 Dosage form of the product

3.3 Strength of the product

3.4 Therapeutic use(s)

3.5 Visual description of the

3.6 Type of container

3.7 Pack size(s)

3.8 Proposed Shelf life (in months)

3.9 Storage conditions

3.10 Country of origin

3.11 Status of registration of the product in the country of origin, authorization/registration number.

4. COMPOSITION OF THE PRODUCT

List all active ingredient(s) and all non active ingredient(s) used

(i) Scientific or Botanical Name of the plant(s)

(ii) The common name or synonym is the English name.

(iii) Part of Plant used:

(iv) Specification (USP, BP, or In house):

(v) Quantity per dosage unit:

(vi) Chemical Constituent(s):

(vii) Reason for inclusion:

5. QUALITY CONTROL OF RAW MATERIALS

5.1 Botanical identification of the Plant used

5.1.1 Botanical name

5.1.2 Brief description of the living plant

5.1.3 Macroscopic identification

5.1.4 Microscopic identification

5.2 Geographical source of the plant used

5.3 Harvesting and collection of the plant

5.4 Method of drying

5.5 Storage and preservation of plant material

5.6 Evaluation of plant materials

5.6.1 Purity tests

5.6.2 Qualitative and quantitative tests of the plant materials

6. QUALITY CONTROL OF THE FINISHED PRODUCT**6.1 Specification of the Finished Product:**

1) Microbiological contamination and tests for other toxins

2) Uniformity of weight (for tablets, single-dose powders, suppositories, herbal tea in sachets and capsules, etc.), disintegration time (for tablets, capsules, suppositories and pills), hardness and friability (for example, uncoated tablets), viscosity (for internal and external fluids), consistency (semisolid preparations), and dissolution (tablets or capsules), if applicable.

3) Physical appearance such as colour, odour, form, shape, size and texture

4) Loss on drying or water content

5) Identity tests, qualitative determination of relevant substances of the plants (e.g. fingerprint chromatograms)

6) Quantification of relevant active ingredients if they are identified and the adequate analytical methods are available

7) Limit tests for residual solvents

6.2 Brief Description of the Manufacturing Procedure and In Process Quality Controls**6.3 Analysis of the Finished Product**

.4 Packaging and Labeling of the Finished Product (include package insert)

The print size and color should be legible and in English or Kiswahili. The product label should have the following:

- a) Name of the product
- b) Composition: The quantitative list of main active ingredients including the common English name of the relevant plants. If the product is imported, plant name should be mentioned along with botanical name
- c) Dosage form
- d) Pack size
- e) Name of manufacturer and physical address of the manufacturing site
- f) Lot/Batch number
- g) Manufacture date and expiry date
- h) Storage conditions

PACKAGE INSERT

This should contain the following information in English:

- a) Name and description of the product
- b) Composition
- c) Pharmacological properties, where information is available
- d) Therapeutic indications
- e) Dosage: the minimum and maximum as well as average dosage levels, must be stated (if appropriate, specified for children and the elderly).
- f) Contraindications/precautions, Interactions and Cautions/warnings
- g) Withdrawals periods for veterinary herbal and complementary products
- h) Name and address of the manufacturer
- i) Overdose and treatment
- j) Adverse reactions
- k) Special considerations e.g. vaginal, rectal, and urethral preparations

l) Storage conditions.

m) Main vehicle/base

7. STABILITY STUDIES OF THE FINISHED PRODUCT

The physical and chemical stability of the product in the marketing container should be determined under defined storage conditions to support the shelf-life. This section should include a summary of the studies undertaken (environmental conditions, batches, analytical procedures) and a brief discussion of the results and conclusions, the proposed storage conditions or shelf-life. Long term stability studies should follow ICH guidelines.

8. SAFETY AND EFFICACY INFORMATION

8.1 SAFETY OF THE PRODUCT

8.1.1 Ethno-medical information (Literature search): The applicant should provide proof of long period use by different communities including folklore, anthropological studies etc.

8.1.2 Pharmacological literature review: The applicant should provide information on:

(i) Pharmacological properties: desirable and undesirable effects associated with the use of the herbal or complementary product including Adverse/Side Effects, Contraindications, Warning and precautions.

(ii) Dosage regimen: Therapeutic prescribed amount of the medicine to be administered to the patient. The measures and age group should be included.

(iii) The onset and duration of effect to support the proposed route of administration and frequency of dosage of the medicinal product should be provided.

8.1.3 Pharmacotoxicological Studies: The applicant should provide a report on Pharmacotoxicological data which should include pharmacological activity, acute, sub-acute, chronic and sub-chronic tests.

The Pharmacotoxicological test reports should be submitted from but not limited to any of the under listed institutions:

(i) Kenya Medical Research Institute

(ii) University of Nairobi, School of Pharmacy and Faculty of herbal Medicine.

8.2 EFFICACY OF THE PRODUCT

Efficacy refers to the successful prevention, diagnosis and treatment of physical and psychological illness; improvement of symptoms of illness; as well as beneficial alteration or regulation of the physical and mental status of the body and mind. The information of proof of efficacy should include any of the following;

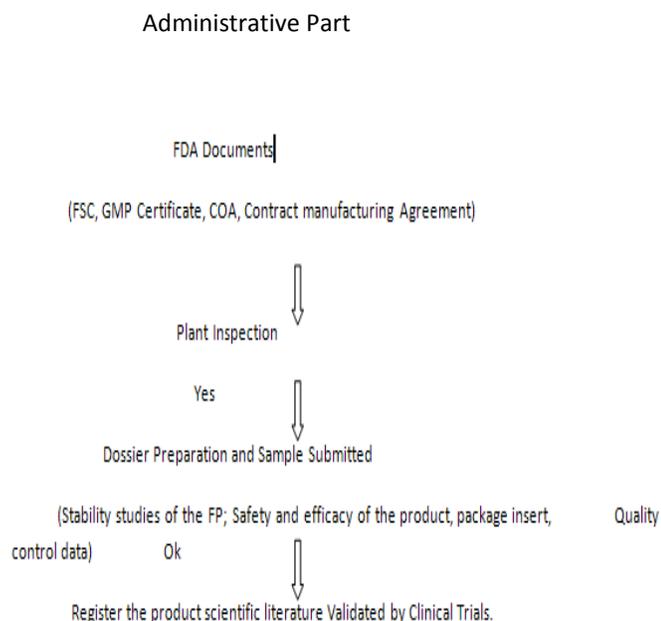
- Individual experiences recorded in reports from registered medical practitioner or
- Experiences from herbal or complementary practitioners or
- Experiences from treated patients.
- Clinical evidence will be required in cases where traditional use has not been Documented.
- Scientific literature validated by clinical trials

	Nigeria	Kenya
FDA Documents	Free Sale Certificate (original)(legalized/Notarized) GMP Certificate of Manufacturing License (Original)(legalized) Contract Manufacturing Agreement Comprehensive Certificate of analysis Certificate of Business Incorporation with the corporate affairs commission in Nigeria Certificate of Registration of Brand Name with trademark Registry (where necessary)	Free Sale Certificate (original)(legalized/Notarized) GMP Certificate of Manufacturing License (Original)(legalized) COA Status of registration of the product in the country of origin, authorization/registration number
Dossier	Application form Administrative dossier Herbal dossier Clinical dossier Stability tests on the finished product	Application form Administrative dossier Herbal dossier Clinical dossier Stability tests on the finished product Summary of product characteristics
Sample Requirement	Actual sample Sample quantity: 10 Units Packaging: English language Patient information leaflet	Actual sample Sample quantity: 3 units Packaging: English language Patient information leaflet
Clinical Trials	Safety & efficacy data required.	Clinical & non- clinical or toxicological data required.
Research paper	Plant Research Articles	Scientific literature validated by clinical trials

REGISTRATION PROCESS FOR AFRICAN REGIONS

Nigeria

Kenya

**Figure 1: Registration Process For African Region****CONCLUSION:**

Different countries have different regulatory guideline for registration of herbal formulation. Some of the data required by some countries are practically impossible to provide and hence their guideline also differ significantly from each other. Hence need to synchronize registration process throughout the world to reduce the expenses as well as time to export herbal formulation.

ACKNOWLEDGEMENT: We are acknowledging Dr. K. Pundrikakshudu, Director of L.J.Institute of Pharmacy for providing us facilities and guidance.

REFERENCES

- 1) Sachan V and Gutam R, "Regulatory issue for Herbal product-A review". *pharmainfo.net*. 2009, www.pharmainfo.net/justvishal/publication/Regulatory-issue-herbal-product-review.
- 2) "The features & differences between regulated, semi-regulated and unregulated pharmaceutical markets". October 2013, <http://answer.com/question/index?qid-20071005015332AAMsuzB>

3) Jayakumar P B, "Small drug firms explore semi-regulated markets". *Business Standard*. 2007,8. www.business-standard.com/article/sme/Small-drug-firms-explore-semi-regulated-markets-10706080113-1.html.

4) Guidelines for the Appropriate use of Herbal Medicines, "Essential medicines and Health product Information portal-A world Health organization resource". September 2013, <http://apps.who.int/medicinedocs/en/d/Jh2945e>.

5) National Policy on Traditional Medicine and Regulation of Herbal Medicines Report of a WHO Global Survey. "Essential medicines and Health product Information portal-A world Health organization resource". September 2013, <http://apps.who.int/medicinedocs/en/d/Js7916e/10.html#Js7916e.10>

6) "Legal Status of Traditional Medicine and Complementary/Alternative Medicine: A Worldwide Review". September 2013, <http://apps.who.int/medicinedocs/pdf/h2943e/h2943e.pdf>

7) "National Agency For Food And Drug Administration And Control of Nigeria". September 2013, www.nafdac.gov.ng.

8) Kenya, "Herbal Guideline". December 2013, pharmacyboardkenya.org/downloads/title=guideline.pdf

